Once-daily evening administration of mometasone furoate in asthma treatment initiation

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Background: In a previous study, a 200-μg once-daily evening dose of mometasone furoate dry powder inhaler (DPI) was effective in patients with asthma previously taking inhaled corticosteroids. No studies have been conducted to test the effect of a once-daily evening dose in patients previously using only short-acting β_2-adrenergic agonists (SABAs) for symptom relief.

Objective: To evaluate the effectiveness of mometasone furoate DPI administered once daily in the evening as initial controller therapy in patients previously using SABAs alone for asthma.

Methods: Patients with mild-to-moderate persistent asthma from 18 US centers participated in a 12-week, randomized, double-blind, placebo-controlled study. Patients received either mometasone furoate DPI, 200 μg, or placebo once daily in the evening. The primary efficacy variable was the change in forced expiratory volume in 1 second from baseline to the end point (last evaluable visit). Other measurements included forced vital capacity, forced expiratory flow between 25% and 75%, morning and evening peak expiratory flow, asthma symptoms, use of albuterol, nocturnal awakenings, physicians' evaluation of response to therapy, and time to asthma worsening.

Results: At the end point, the mean increase in forced expiratory volume in 1 second relative to baseline for the mometasone furoate DPI group of 0.43 L (16.8%) was significantly greater than that for the placebo group of 0.16 L (6.0%) ($P < .01$). Morning peak expiratory flow, forced vital capacity, and forced expiratory flow between 25% and 75% also significantly improved with mometasone furoate DPI treatment relative to placebo ($P < .01$). Once-daily dosing with mometasone furoate DPI was well tolerated.

Conclusion: Mometasone furoate DPI (200 μg) administered once daily in the evening significantly improves pulmonary function in patients previously using SABAs alone for asthma control.

Ann Allergy Asthma Immunol. 2006;96:533–540.

INTRODUCTION

Inhaled corticosteroids (ICSs) are a major long-term controller therapy for patients with mild, moderate, or severe persistent asthma.[1–3] Inhaled corticosteroids reduce bronchial inflammation, and studies suggest that they reverse the airway remodeling that occurs across time with asthma.[4] Despite the availability of effective ICS therapy, however, poor adherence remains a pervasive obstacle to improving outcomes in many patients with asthma.[5] Typically, ICSs are administered in regimens that require multiple daily doses (at least twice daily), which can diminish adherence and create a barrier to effective disease control. Simplification of the treatment regimen tends to promote improved adherence, and most patients prefer once-daily dosing to twice-daily dosing.[6,7] Currently, the only ICS approved in the United States for once-daily administration in the treatment of asthma is budesonide, but only for patients already well controlled with twice-daily budesonide.[8] Mometasone furoate dry powder inhaler (DPI) is an ICS approved for once-daily administration as initial controller therapy and as maintenance therapy in patients previously taking stable doses of ICSs.[9]

A previous dose-ranging study[10] demonstrated that mometasone furoate DPI, 200 μg administered twice daily, was effective and well tolerated in patients with moderate persistent asthma previously using other ICSs. Subsequent studies involving patients previously using only short-acting β_2-adreneric agonists (SABAs) to treat asthma symptoms[11,12] and patients previously using ICSs[13] demonstrated that mometasone furoate DPI, 400 μg administered once daily in the morning, was effective; it was also shown to be comparable with mometasone furoate DPI, 200 μg administered twice daily, in the studies that included a twice-daily dosing arm.[11,13] The study by Noonan et al[13] indicated that mometasone furoate DPI administered at a low dose of 200 μg once daily in the evening was more effective than the same dose of mometasone furoate DPI administered in the morning. Studies[14,15] of mometasone furoate DPI have also shown that

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Received for publication December 13, 2004.
Accepted for publication in revised form June 20, 2005.

400 μg administered once daily in the evening is as effective as 200 μg administered twice daily.

Indeed, evidence suggests that the timing of single doses of ICSs may be as important as the amount of the dose regarding the effectiveness of treatment and that evening dosing can be more effective than morning dosing for ICSs.[13,16,17] This finding could be due to the normal circadian rhythms associated with the daily waxing and waning of the symptoms of asthma and those of pulmonary function and the related mechanisms of inflammation.[18–20] The circadian rhythms of proinflammatory cytokines, such as interferon-γ, tumor necrosis factor α, and interleukins 1 and 12, may exacerbate the nocturnal or early morning manifestations of asthma.[21] An evening dose of corticosteroids, therefore, could suppress the diurnal increase of these cytokines, leading to superior disease management. Innate cortisol secretion also shows circadian variations. Peak secretion occurs early in the morning, with activity-related fluctuations during the day and less fluctuation, with lower levels of serum cortisol, at night.[22]

The purpose of this study was to directly compare the effectiveness of mometasone furoate DPI, 200 μg administered once daily in the evening, with placebo in patients previously using only SABAs for control of their asthma.

METHODS

Patients

The study population consisted of 196 adult and adolescent patients (12 years and older) who had a history of asthma for at least 6 months. Patients must have been using only SABAs for 2 weeks before screening and must have been using albuterol at least 3 times a week on average between the screening and baseline visits.

Patients were to demonstrate a baseline forced expiratory volume in 1 second (FEV_1) of 55% to 85% of the normal predicted values after albuterol was withheld for 6 hours and reversibility of airway obstruction by an increase in absolute FEV_1 of 12% or more and an absolute volume increase of at least 200 mL at screening or in the past 12 months. Patients were excluded if they had received treatment with ICSs in the previous 3 months; required daily or alternate-day oral corticosteroid therapy for more than a total of 14 days during the previous 6 months; received treatment with methotrexate, cyclosporine, gold, or other immunosuppressive agents for the control of asthma in the past 3 months; required emergency hospital treatment for asthma twice in the previous 6 months; been hospitalized for an asthma exacerbation in the previous 3 months; or required intubation for asthma in the previous 5 years. Furthermore, patients with clinical evidence of other respiratory diseases (eg, emphysema or chronic bronchitis) or any clinically significant disease other than asthma were excluded, as were patients who were current smokers or who had smoked in the previous 6 months. Premenarchal, pregnant, and breastfeeding women were excluded, and women of childbearing potential were required to use an acceptable method of birth control during the study.

Study Design

This double-blind, parallel-group, placebo-controlled, randomized study was conducted at 18 medical centers across the United States. The protocol and the patient informed consent forms were reviewed by institutional review boards responsible for each study center. Written informed consent was obtained from each patient and from the parent or guardian of each patient younger than 18 years. The study was conducted in accordance with Good Clinical Practice.

A screening visit (visit 1), which included a physical examination, spirometry, and training in the use of the peak flow meter (Personal Best; Respironics, Murrysville, PA), preceded the treatment period by 7 to 14 days (run-in period). At the screening visit, the patient was provided with a diary and an albuterol sulfate (Proventil; Schering Corp, Kenilworth, NJ) metered-dose inhaler for rescue medication. Nebulized β_2-adrenergic agonists and albuterol were permitted as rescue medication but were withheld for at least 6 hours before study visits. All other asthma medications, including long- and short-acting oral and inhaled β_2-adrenergic agonists, leukotriene modifiers, theophylline, and ICSs, were prohibited during the run-in period and for the duration of the study. Daily diary cards were used for the duration of the study to record morning and evening peak expiratory flow (PEF), number of albuterol inhalations, symptoms of asthma, number of nocturnal awakenings requiring the use of albuterol, adverse events, and daily medication use, including study medication.

At baseline (visit 2), patients were randomly assigned to 1 of the 2 treatment groups according to a computer-generated code. Each patient received a single DPI device for use throughout the entire study and instructions for its proper use. The active mometasone furoate DPI device was indistinguishable from the placebo DPI. Study medication was to be taken once daily as 1 inhalation from a mometasone furoate DPI delivering 200 μg per puff or as placebo (lactose only) in the evening; no other explicit directive was given regarding the timing of the evening dose.

At all the visits (screening, baseline, and weeks 1, 2, 4, 8, and 12), vital signs were obtained and oropharyngeal examinations and spirometry were performed. Visits were preferably to be completed at approximately the same time of day, with the same individual performing a given function throughout a patient's participation in the study. Daily diary data were reviewed. During treatment, the visits also included physicians' assessments of response to therapy.

Efficacy Assessments

The primary efficacy variable was the mean change from baseline to the end point (the last evaluable treatment time) in absolute FEV_1. Secondary efficacy variables included mean change from baseline in forced vital capacity (FVC), forced expiratory flow between 25% and 75% ($FEF_{25\%-75\%}$), and morning and evening PEF; asthma symptom scores; rescue albuterol use; nocturnal awakenings due to asthma that re-

quired albuterol use; physician assessments of response to therapy; and time to worsening of asthma.

Individual asthma symptoms (wheezing, difficulty breathing, and cough) were rated for severity by the patient using a 4-point scale (0 = none, 1 = noticeable, 2 = annoying, and 3 = very uncomfortable) and were recorded in a diary twice daily (morning and evening). During scheduled visits, the physicians numerically rated the response to therapy (1 = much improved, 2 = improved, 3 = no change, 4 = worse, and 5 = much worse) compared with the level of symptoms at baseline.

Time to worsening of asthma was defined as the first occurrence of any of the following: a 20% or greater decrease in FEV_1 from baseline; clinical asthma exacerbation requiring emergency treatment, hospital admission, or treatment with asthma medications in addition to those permitted in the protocol; a 25% or greater decrease in morning or evening PEF from the mean baseline morning value for any 2 consecutive days; more than 12 inhalations of rescue albuterol per day for 2 consecutive days; or more than 2 treatments with nebulized β_2-adrenergic agonists on 2 consecutive days. Patients were discontinued from the study if they met any of the previous criteria for asthma worsening.

Safety Assessments

A complete medical history and physical examination were performed at the screening visit. An electrocardiogram was performed if the results of a previous electrocardiogram (in the past 30 days) were not available. A chest radiograph was obtained if the results of one taken in the previous year were not available. Clinical laboratory tests, including a complete blood cell count, blood chemistry, and urinalysis, were performed at the screening visit and at the final visit (week 12). All the patients were monitored closely for adverse events and for clinical asthma exacerbations that would require emergency treatment, hospitalization, or treatment with additional asthma medications (other than the SABAs permitted by the protocol). At all the visits, vital signs were measured and an oropharyngeal examination was performed.

Statistical Analysis

The primary measure of efficacy was the mean change in FEV_1 from baseline to the end point (last evaluable visit). The study was designed to enroll 80 patients per treatment group to detect, with 95% power at a .05 significance level, a clinically meaningful mean change from baseline in FEV_1 (0.26 L) comparing mometasone furoate DPI, 200-μg once-daily evening treatment, with placebo use. The primary efficacy analyses were based on all randomized patients who received at least 1 dose of study medication and who had postbaseline data (intention-to-treat principle).

All the efficacy variables were analyzed using 2-way analysis of variance (ANOVA), which extracted sources of variation due to treatment and medical center. Pairwise comparisons were performed using least square means from the ANOVA, with a $P < .05$ significance level, without adjustment for multiple comparisons. In addition to the analysis at the end point, the 2 treatment groups were compared with respect to the change from baseline using the same 2-way ANOVA. The evaluation of response to therapy of the percentage of patients demonstrating improvement from baseline was analyzed using the Fisher exact test. Kaplan-Meier survival estimates were calculated for the time to asthma worsening.

RESULTS

Patient Population

A total of 196 patients were randomized to treatment at 18 medical centers in the United States. All but 1 patient received at least 1 dose of study medication; therefore, 195 patients were included in the intention-to-treat population. The baseline demographic and asthma characteristics of these 2 groups were comparable (Table 1). Most patients (88%) completed the full 3 months of treatment in the study, and all but 1 (in the placebo group) were adherent (defined as having taken $\geq$75% of the scheduled doses) to study treatment administration. A total of 23 patients discontinued treatment before scheduled completion: 11 (11%) in the mometasone furoate DPI group and 12 (13%) in the placebo group (Table 2).

Pulmonary Function

There was no significant difference between treatment groups in mean FEV_1 at baseline (Table 1). The increase from baseline in FEV_1 was greater for the mometasone furoate DPI group than for the placebo group at all times, starting with the first observation at week 1 (Fig 1). Mean FEV_1 increased by 16.8% between baseline and the end point in the mometasone furoate DPI group compared with 6.0% in the placebo group ($P < .01$) (Table 3).

Results of other assessments of pulmonary function were consistent with the improvement in FEV_1 observed for the mometasone furoate DPI, 200 μg once daily, treatment (Table 3). Improvements in FVC, $FEF_{25\%-75\%}$, morning PEF, and evening PEF at the end point were significantly greater for

Table 1. Baseline Demographic and Disease Characteristics by Study Group

	Mometasone furoate DPI group (n = 100)*	Placebo group (n = 95)
Age, mean (range), y	29.7 (12–65)	28.6 (12–66)
Sex, M/F, No.	47/53	47/48
Race, white/black/other, No.	79/7/14	75/13/7
Weight, mean, lb	168.6	167.1
Duration of asthma, mean, y	15.4	15.9
FEV_1, mean ± SEM, L	2.55 ± 0.06	2.64 ± 0.06
Morning PEF, mean ± SEM, L/min	370 ± 9	360 ± 9

Abbreviations: DPI, dry powder inhaler; FEV_1, forced expiratory volume in 1 second; PEF, peak expiratory flow.

* Patients took 200 μg once daily in the evening.

time of dosing occurred between 8 and 11 PM, with the greatest percentage taking place at approximately 10 PM. The numbers of patients taking mometasone furoate DPI earlier than approximately 9 PM and later than approximately 11 PM were too low to permit subset analysis. The dosing times in the present study are likely to be similar because the age range of the population was identical to that of the previous study.

In summary, a relatively low dose of mometasone furoate DPI, 200 μg given once daily in the evening, significantly improved pulmonary function compared with placebo use in a population of asthmatic patients previously treated with SABAs alone. Consistent with previous studies,[10–13] mometasone furoate DPI was well tolerated. Once-daily dosing with mometasone furoate combined with a DPI designed to improve patient compliance[30,31] should provide advantages to enhance asthma management.

ACKNOWLEDGMENTS

We thank the following investigators for their contributions to this study: D. Bernstein, MD (Cincinnati, OH); A. DeGraff, Jr, MD (Hartford, CT); D. Dvorin, MD (Forked River, NJ); F. Hampel, Jr, MD (New Braunfels, TX); S. D. Miller, MD (North Dartmouth, MA); A. Nayak, MD (Normal, IL); M. Noonan, MD (Portland, OR); J. Pinnas, MD (Tucson, AZ); N. Segall, MD (Atlanta, GA); E. Schenkel, MD (Easton, PA); E. Sher, MD (West Long Branch, NJ); D. R. Webb, MD (Kirkland, WA); and S. Weinstein, MD (Huntington Beach, CA). We also thank Lucy Shneyer for biostatistical analysis of the clinical study data and Ken Kauffman for editorial assistance.

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Effects of treatment with mometasone furoate dry powder inhaler in children with persistent asthma

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Background: Mometasone furoate dry powder inhaler (DPI) has been shown to effectively treat asthma in children.

Objective: To evaluate the efficacy and safety of 2 dosing regimens of mometasone furoate DPI in the treatment of mild-to-moderate persistent asthma in children previously using inhaled corticosteroids (ICSs).

Methods: A 12-week, multicenter, double-blind, parallel-group, placebo-controlled study evaluated 2 dosing regimens of mometasone furoate DPI (100 μg every evening and 100 μg twice daily) in 296 children 4 to 11 years old with asthma previously using ICSs. The primary efficacy variable was the change in percentage of predicted forced expiratory volume in 1 second (FEV_1) from baseline to end point. Secondary efficacy variables included absolute FEV_1, forced expiratory flow between 25% and 75% forced vital capacity, morning and evening peak expiratory flow, asthma symptom scores, albuterol use, nocturnal awakenings, response to therapy, and health-related quality of life.

Results: Mean changes from baseline at end point in predicted FEV_1 were 4.73 and 5.52 percentage points for mometasone furoate DPI, 100 μg every evening and 100 μg twice daily, respectively, the difference of which was not significant, and −1.77 percentage points for placebo ($P \leq .002$). Significant improvements in secondary efficacy variables were also observed for both mometasone furoate DPI treatments over placebo. Both mometasone furoate DPI doses were well tolerated, and no significant differences were noted among the 3 treatment groups in adverse event reporting.

Conclusions: Both mometasone furoate DPI doses were well tolerated and significantly improved lung function, maintained effective asthma control, and improved quality of life in children with asthma.

Ann Allergy Asthma Immunol. 2006;97:672–680.

INTRODUCTION

An estimated 6.1 million children younger than 18 years in the United States have asthma.[1] Inhaled corticosteroids (ICSs) are the preferred treatment recommended by the National Heart, Lung, and Blood Institute for children with mild, moderate, and severe persistent asthma.[2] As demonstrated in the Childhood Asthma Management Program study,[3] improvements with ICS treatment in children 5 to 12 years of age with asthma included reduced airway hyperresponsiveness, improved pulmonary function and symptom scores, fewer courses of oral corticosteroids, and fewer urgent care visits or hospitalizations. These improvements in asthma control were reversed when treatment was discontinued, suggesting that treatment did not modify underlying disease progression. A long-term study[4] in younger children (2–3 years of age) has been conducted to determine whether earlier intervention can prevent disease progression. However, relatively few well-controlled studies evaluating the effects of ICSs on children's functional status or quality of life in the treatment of asthma have been published.[5–8]

Mometasone furoate is a potent corticosteroid that is available worldwide in dermatologic and intranasal formulations for use in children 2 years or older.[9] As an aqueous nasal spray, mometasone furoate has exhibited negligible systemic bioavailability, with no effects on growth velocity in children[10] or on suppression of the hypothalamic-pituitary-adrenal axis.[11,12]

Mometasone furoate dry powder inhaler (DPI) is currently available in 42 countries for the treatment of mild-to-severe persistent asthma in patients 12 years or older. Randomized, placebo-controlled studies[13–16] have demonstrated that mometasone furoate DPI is well tolerated and provides effective asthma control at doses of 200 or 400 μg once daily in the evening or as divided doses (200 μg twice daily) in adults with mild-to-moderate persistent asthma who had previously been taking ICSs to control their asthma. These studies found that once-daily, evening treatment with mometasone furoate DPI not only improved lung function but also reduced symptoms, albuterol use, and nocturnal awakenings compared with placebo. Two of the studies[16,17] also evaluated the effects of treatment on health-related quality of life (HRQOL) and

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This study was supported by Schering-Plough Corp.
Received for publication October 19, 2005.
Accepted for publication in revised form December 6, 2005.

found that mometasone furoate DPI treatment significantly improved HRQOL. A randomized, placebo-controlled study[18] in children 4 to 11 years of age with persistent asthma found that treatment with mometasone furoate DPI, 100 μg once daily in the morning, had efficacy comparable with treatment with 200 μg once daily in the morning. This pediatric study differed from the adult studies mentioned previously in that the once-daily doses were taken in the morning rather than in the evening; a once daily in the evening dosing regimen of mometasone furoate DPI had not yet been evaluated in an efficacy study involving children younger than 12 years. The purpose of this study was to therefore compare the efficacy and safety of mometasone furoate DPI, 100 μg once daily in the evening and 100 μg twice daily, with placebo in children with mild-to-moderate persistent asthma previously controlled with ICSs and to evaluate the efficacy and safety of mometasone furoate DPI, 100 μg once daily in the evening vs 100 μg twice daily.

METHODS

The protocol and informed consent forms for this study were approved by an authorized institutional review board for each study center before implementation. The study was conducted in compliance with Good Clinical Practice and International Conference on Harmonization guidelines and under the principles of the Helsinki Declaration.

Participants

Pediatric patients 4 through 11 years old with at least a 6-month history of diagnosed asthma who required daily treatment with an ICS for at least 60 days were enrolled. Participants were required to demonstrate a forced expiratory volume in 1 second (FEV_1) of 60% or greater and 85% or less of the predicted normal values at the screening and baseline visits and an increase in absolute FEV_1 of 12% or greater after reversibility testing with albuterol.

Individuals were excluded if they met any of the following criteria: use of nebulized β_2-agonists or long-acting inhaled β_2-agonists, hospitalization due to asthma in the past 3 months, ventilator support for respiratory failure secondary to asthma in the past 5 years, systemic corticosteroids for more than 15 days during the 6 months before the screening visit, a change in FEV_1 of 20% or greater between the screening and baseline visits, and use of more than 12 inhalations per day of rescue medication (or 3 nebulizer treatments) on 2 consecutive days between the screening and baseline visits.

Study Design

This was a multicenter, randomized, double-blind, parallel-group, placebo-controlled, 12-week treatment efficacy and safety study, with participants randomly assigned (in a 1:1:1 ratio) to receive mometasone furoate DPI, 100 μg once daily in the evening or 100 μg twice daily, or placebo. Primary comparisons were made between the mometasone furoate DPI treatment groups and the placebo group. Pairwise comparisons between all treatment groups were also performed if the primary comparison was statistically significant. Written informed consent was obtained from the patient's parent or guardian, and informed assent was also obtained from patients 6 or 7 years and older before initiation of any protocol-specified procedures.

Spirometry to measure FEV_1, forced vital capacity (FVC), and forced expiratory flow between 25% and 75% ($FEF_{25\%-75\%}$) was performed at all study visits. At all the study centers, Polgar ranges[16] were used for all the participants. Spirometry was performed using spirometers that met the American Thoracic Society recommendations.[19] The participant's response to therapy was evaluated by the physician or a designee at each follow-up visit by comparing the current level of symptoms with those noted at the baseline visit using a 5-point scale (1 = much improved, 2 = improved, 3 = no change, 4 = worse, and 5 = much worse).

An HRQOL questionnaire was completed at baseline and at weeks 8 and 12. This questionnaire was composed of the validated Child Health Questionnaire (CHQ)[17] and a validated version of the Usherwood asthma-specific module.[18] The asthma-specific questionnaire assessed daytime symptoms, nocturnal symptoms, disability, chest pain, and how much asthma interrupts a child's life.

The inclusion of a placebo group was considered justified because patients who experienced clinically significant worsening of asthma were to be discontinued, and participants were permitted to use short-acting β_2-agonists during the study. Patients who experienced a 20% or greater decrease in FEV_1 (absolute value) from the baseline visit or who experienced a clinical asthma exacerbation resulting in hospitalization or treatment with asthma medication not allowed by the protocol were discontinued from the study.

Efficacy

The primary efficacy variable was the mean change from baseline in the percentage of predicted FEV_1 at the end point. Secondary efficacy variables included spirometric test results (absolute FEV_1, FVC, and $FEF_{25\%-75\%}$) and evaluation of response to therapy, numbers of clinically significant asthma exacerbations and asthma worsenings, and time to asthma worsening. The following secondary efficacy variables were recorded on the patient's daily diary card: morning and evening peak expiratory flow (PEF), daytime and nighttime asthma symptoms (wheezing, difficulty breathing, and cough), number of nocturnal awakenings requiring rescue medication use, and amount of rescue medication required daily. Evaluation of HRQOL, including an asthma-specific module, was also a secondary efficacy variable.

Statistical Analyses

Analyses and summaries of all efficacy and safety data were based on the intention-to-treat population, defined as all randomized patients who received at least 1 dose of study treatment. The study was designed to enroll 315 individuals (approximately 105 per treatment group) who met the criteria for evaluation of the primary efficacy end point. The sample size was chosen to detect (with 90% power and a 2-sided .05

significance level) a clinically meaningful pairwise difference (≥7.0) in the percentage of predicted FEV_1 mean change from baseline between either of the mometasone furoate DPI groups and the placebo group. The primary efficacy variable was change from baseline in the percentage of predicted FEV_1 at the end point. The primary efficacy analysis at the end point and at each visit was based on a 2-way analysis of variance.

RESULTS

Participants

Children 4 to 11 years of age (n = 296) were randomized to treatment. The duration of the diagnosed asthma ranged from 1 to 11 years (Table 1). The treatment groups' demographics were similar for most baseline characteristics, including predicted FEV_1 (Tables 1 and 2).

Pulmonary Function

The change in the percentage of predicted FEV_1 from baseline to the end point showed a significantly superior treatment response for both mometasone furoate DPI treatment groups compared with the placebo group ($P \leq .002$). Least squares mean changes at the end point in the percentage of predicted FEV_1 were 4.73 and 5.52 for the mometasone furoate DPI, 100 μg once daily in the evening and 100 μg twice daily, groups, respectively, compared with −1.77 for the placebo group. The slight difference between the mometasone furoate DPI groups was not statistically significant ($P = .70$). Both mometasone furoate DPI treatment doses were more effective compared with placebo in improving lung function at the end point based on FEV_1 ($P < .001$), FVC ($P \leq .04$), and $FEF_{25\%-75\%}$ ($P < .001$) (Table 3). No significant differences were observed between the 2 mometasone furoate DPI groups in change from baseline at end point.

Response to Therapy

At the end point, the percentage of patients judged to be improved or much improved was 68% with mometasone furoate DPI, 100 μg once daily in the evening; 62% with mometasone furoate DPI, 100 μg twice daily; and 44% with placebo. The differences between both mometasone furoate DPI groups and the placebo group were statistically significant ($P \leq .02$).

Diary Data

Improvements in morning and evening PEF (Table 4) were significantly greater at the end point in both mometasone furoate DPI groups than in the placebo group ($P < .001$). Overall, no significant differences were observed for improvements in morning and evening PEF between the mometasone furoate DPI groups.

Mean asthma symptom scores for wheezing, difficulty breathing, and cough were generally low (<1) at baseline, and most patients continued to report no or low symptom scores throughout treatment. At the end point, mean values decreased for all 3 symptom scores in the mometasone furoate DPI groups and increased in the placebo group. Owing to the low symptom scores and the low number of nocturnal awakenings at baseline, no inferential analyses of these data were conducted.

Overall, rescue medication use was low throughout the study. At the end point, however, mean use of rescue medication had decreased by 0.4 to 0.5 inhalations per day in the mometasone furoate DPI groups compared with an increase of 0.3 inhalations per day in the placebo group ($P \leq .006$).

Table 1. Baseline Demographics for All Randomized Participants

Demographics	Mometasone furoate DPI, 100 μg, group		Placebo group (n = 99)
	Once daily in the evening (n = 98)	Twice daily (n = 99)	
Age, mean ± SD (range), y	9.0 ± 1.8 (4–11)	8.7 ± 1.8 (4–11)	8.2 ± 1.9 (4–11)
Age, No.			
4–5 y	5	5	4
6–11 y	93	94	95
Sex, No. (%)			
F	41 (41.8)	32 (32.3)	36 (36.4)
M	57 (58.2)	67 (67.7)	63 (63.6)
Race, No. (%)			
White	56 (57.1)	63 (63.6)	60 (60.6)
Black	16 (16.3)	11 (11.1)	12 (12.1)
Hispanic	22 (22.4)	22 (22.2)	24 (24.2)
Asian	1 (1.0)	1 (1.0)	0
Native American	1 (1.0)	2 (2.0)	0
Other	2 (2.0)	0	3 (3.0)
Body weight, mean ± SD, kg	35.4 ± 10.9	35.2 ± 11.3	33.7 ± 12.7
Height, mean ± SD, cm	136.1 ± 11.9	134.8 ± 12.5	132.5 ± 13.4
Duration of asthma, mean ± SD (range), y	5.9 ± 2.7 (1–11)	5.8 ± 2.7 (1–11)	5.3 ± 2.7 (1–10)

Abbreviation: DPI, dry powder inhaler.

Table 2. Baseline Spirometry Results and ICS Use

	Mometasone furoate DPI, 100 μg, group		Placebo group (n = 99)
	Once daily in the evening (n = 98)	Twice daily (n = 99)	
FEV_1, mean, L	1.60	1.57	1.45
FEV_1, mean, % of predicted	79.2	79.7	77.3
Morning PEF, mean, L/min	237.0	237.7	210.9
Baseline ICS use			
Flunisolide			
No. of patients	2	0	1
Mean, μg/d	1,000	NA	1,000
Triamcinolone acetonide			
No. of patients	6	1	5
Mean (range), μg/d	466.7 (400–800)	400	400 (200–800)
Beclomethasone dipropionate			
No. of patients	17	20	18
Mean (range), μg/d	230.1 (84–400)	244.5 (84–400)	200.2 (80–400)
Budesonide			
No. of patients	25	18	23
Mean (range), μg/d	432.0 (200–800)	466.7 (200–800)	504.3 (200–800)
Fluticasone propionate			
No. of patients	48	60	52
Mean (range), μg/d	161.4 (88–440)	173. (88–264)	172.7 (88–264)

Abbreviations: DPI, dry powder inhaler; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; NA, not applicable; PEF, peak expiratory flow.

Table 3. Spirometry Results (Intent-to-Treat Population)*

	Mometasone furoate DPI, 100 μg, group		Placebo group (n = 99) (C)	95% CI
	Once daily in the evening (n = 98) (A)	Twice daily (n = 99) (B)		
FEV_1, % of predicted				
Baseline	79.21	79.67	77.31	
Change at end point	4.73	5.52	−1.77	
% Change at end point	8.3	8.8	0	A-B, −4.86 to 3.29, $P = .70$; A-C, 2.44 to 10.56, $P = .002$; B-C, 3.22 to 11.35, $P < .001$
FEV_1, L				
Baseline	1.60	1.57	1.46	
Change at end point	0.09	0.09	−0.04	
% Change at end point	8.3	8.8	0	A-B, −0.08 to 0.07, $P = .92$; A-C, 0.05 to 0.20, $P < .001$; B-C, 0.06 to 0.21, $P < .001$
FVC, L				
Baseline	2.01	2.00	1.88	
Change at end point	0.09	0.09	−0.01	
% Change at end point	7.4	6.7	3.7	A-B, −0.09 to 0.10, $P = .95$; A-C, 0.01 to 0.20, $P = .03$; B-C, 0.01 to 0.19, $P = .04$
$FEF_{25\%-75\%}$				
Baseline	1.53	1.47	1.35	
Change at end point	0.14	0.19	−0.12	
% Change at end point	14.0	24.0	0.5	A-B, 0.20 to 0.10, $P = .49$; A-C, 0.11 to 0.41, $P < .001$; B-C, 0.16 to 0.46, $P < .001$

Abbreviations: CI, confidence interval; DPI, dry powder inhaler; $FEF_{25\%-75\%}$, forced expiratory flow between 25% and 75%; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

* Values are given as least squares means.

Table 4. Results From Diary Data (Intention-to-Treat Population)*

	Mometasone furoate DPI, 100 μg, group		
	Once daily in the evening (n = 98)	Twice daily (n = 99)	Placebo group (n = 99)
Morning PEF, L/min			
Baseline	237.0	237.7	210.9
Change at end point	16.3	11.2	−6.9
Evening PEF, L/min			
Baseline	243.3	244.3	218.6
Change at end point	14.9	12.9	−5.6
Daytime asthma symptom scores			
Wheezing			
Baseline	0.35	0.29	0.33
Change at end point	−0.06	−0.06	0.10
Difficulty breathing			
Baseline	0.39	0.35	0.38
Change at end point	−0.08	−0.03	0.09
Cough			
Baseline	0.53	0.52	0.53
Change at end point	−0.11	−0.08	0.05
Nighttime asthma symptom scores			
Wheezing			
Baseline	0.37	0.27	0.34
Change at end point	−0.09	−0.07	0.08
Difficulty breathing			
Baseline	0.41	0.35	0.40
Change at end point	−0.09	−0.07	0.01
Cough			
Baseline	0.51	0.52	0.53
Change at end point	−0.10	−0.13	0.04

Abbreviations: DPI, dry powder inhaler; PEF, peak expiratory flow.
* Values are given as means.

The difference between the mometasone furoate DPI treatment groups was not significant.

Time to Asthma Worsening

Seventy-nine participants (27%) met 1 or more protocol-specified criteria for worsening of asthma: mometasone furoate DPI, 100 μg once daily in the evening, 17 individuals; mometasone furoate DPI, 100 μg twice daily, 22 individuals; and placebo, 40 individuals. Results of log-rank tests showed that patients in the mometasone furoate DPI groups had a much higher probability of continuing in the study without experiencing asthma worsening than patients in the placebo group (overall $P < .001$). The median time to asthma worsening for the placebo group was 89 days. Because fewer than 50% of the patients in either mometasone furoate DPI groups experienced asthma worsening, median times to worsening for the active treatment groups could not be determined.

Health-Related Quality of Life

Of the 296 randomized individuals, 292 (99%) completed the 28-item short CHQ-parent form (CHQ-PF28) and the asthma-specific questionnaire at baseline and the end point. Mean baseline scores for all the CHQ-PF28 domains, except self-esteem, showed greater burden of disease in study participants compared with the general US population, 5 to 18 years of age. Statistically significant changes from baseline to end point were observed with both mometasone furoate DPI treatments compared with placebo for the physical summary score of the CHQ-PF28 (Table 5) and for the disability, daytime symptoms, and nocturnal symptoms domains of the asthma-specific questionnaire (Table 6). No statistically significant differences were observed between the mometasone furoate DPI treatment groups.

Safety

In general, adverse events (AEs) were mild to moderate in severity, with similar incidences of treatment-emergent AEs in all 3 groups (Table 7). The most frequently reported treatment-emergent AEs in all 3 groups were upper respiratory tract infection and headache. Pharyngitis was reported by 14 patients in the mometasone furoate DPI treatment groups and 9 in the placebo group; oral candidiasis was reported by 1 participant (placebo group). Only 14 participants (4 in the mometasone furoate DPI, 100 μg once daily in the evening, group; 6 in the mometasone furoate DPI, 100 μg twice daily, group; and 4 in the placebo group) reported AEs considered

Table 5. Summary of HRQOL Scores for the CHQ-PF28 Domains*

	Mometasone furoate DPI, 100 μg, group		Placebo group (C)	*P* value (A vs C)
	Once daily in the evening (A)	Twice daily (B)		
Physical summary score†				
No. of patients	95	92	92	
Baseline	42.5	42.1	44.5	
Change at end point	3.4	2.3	−2.1	.002
Physical functioning				
No. of patients	95	93	95	
Baseline	78.6	75.2	81.6	
Change at end point	6.5	7.5	−4.5	.005
Role physical				
No. of patients	97	99	96	
Baseline	83.1	83.2	85.1	
Change at end point	7.7	4.4	−0.1	.08
General health				
No. of patients	97	99	96	
Baseline	51.7	51.3	54.4	
Change at end point	1.3	1.1	−2.1	.03
Bodily pain				
No. of patients	97	99	95	
Baseline	72.6	73.2	77.2	
Change at end point	5.8	−0.4	−6.2	<.001

Abbreviations: DPI, dry powder inhaler; CHQ-PF28, 28-item short Child Health Questionnaire–parent form; HRQOL, health-related quality of life.
* Baseline and change at end point values are given as least squares means. Higher scores indicate better health.
† The physical summary score includes the CHQ-PF28 domains with the largest weighting factors.

Table 6. Summary of HRQOL Scores for the Asthma-Specific Questionnaire*

	Mometasone furoate DPI, 100 μg, group		Placebo group (C)	*P* value (A vs C)
	Once daily in the evening (A)	Twice daily (B)		
Disability				
No. of patients	97	99	96	
Baseline	80.0	80.1	83.0	
Change at end point	9.2	6.8	0.3	<.001
Daytime symptoms				
No. of patients	97	99	96	
Baseline	67.7	68.1	68.6	
Change at end point	10.9	9.5	−1.4	<.001
Nocturnal symptoms				
No. of patients	97	99	96	
Baseline	76.9	74.6	76.0	
Change at end point	7.4	5.2	−3.1	.004
Chest pain				
No. of patients	97	99	94	
Baseline	87.4	85.0	87.5	
Change at end point	4.2	4.6	−0.2	.15
Interrupted child's life				
No. of patients	96	99	96	
Baseline	79.4	80.1	81.8	
Change at end point	9.2	9.7	3.4	.08

Abbreviations: DPI, dry powder inhaler; HRQOL, health-related quality of life.
* Baseline and change at end point values are given as least squares means. Higher scores indicate better health.

to be treatment related. Headache was the only treatment-related AE reported by more than 1 participant in any group. Adverse events led to discontinuation more often in the placebo group than in the mometasone furoate DPI groups.

A review of the serious AEs did not raise any safety concerns. One participant reported a serious AE during the screening phase before treatment with the study drug was initiated, and 5 reported a serious AE during treatment (mo-

Table 7. Treatment-Emergent Adverse Events Reported by at Least 5% of the Participants in Any Study Group*

	Mometasone furoate DPI, 100 μg, group		Placebo group (n = 99)
	Once daily in the evening (n = 98)	Twice daily (n = 99)	
Any adverse event	54 (55)	59 (60)	51 (52)
Headache	5 (5)	12 (12)	14 (14)
Pharyngitis	9 (9)	5 (5)	9 (9)
Upper respiratory tract infection	11 (11)	18 (18)	16 (16)
Allergy	4 (4)	6 (6)	3 (3)
Allergy aggravated	4 (4)	5 (5)	5 (5)
Otitis media	2 (2)	1 (1)	6 (6)
Abdominal pain	6 (6)	6 (6)	2 (2)

Abbreviation: DPI, dry powder inhaler.
* Values are given as number (percentage).

metasone furoate DPI, 100 μg once daily in the evening, 1 individual; mometasone furoate DPI, 100 μg twice daily, 3 individuals; and placebo, 1 individual). The serious AEs reported after randomization were composed of skin burn, abdominal pain, appendectomy, spinal cord surgery, overdose, and atelectasis (the last 2 were reported for the same patient); all were considered unlikely to be related to study treatment.

DISCUSSION

In this study of children with mild-to-moderate persistent asthma previously controlled with ICSs, the efficacy and tolerability of mometasone furoate DPI, 100 μg once daily in the evening, were comparable with those of mometasone furoate DPI, 100 μg administered twice daily, and both mometasone furoate DPI dose regimens were superior to placebo. Based on the primary efficacy outcome, the change in the percentage of predicted FEV_1 between baseline and end point, there was a significantly superior treatment response (>5% increase) in patients treated with the mometasone furoate DPI dose regimens than in those treated with placebo (2% decrease). Mometasone furoate DPI, 100 μg once daily in the evening, was observed to be similar in effectiveness to mometasone furoate DPI, 100 μg twice daily.

Similar results were also observed in the analysis of the other pulmonary function variables, including FEV_1, FVC, $FEF_{25\%-75\%}$, and PEF. The evening PEF results demonstrate the maintenance of effectiveness at the end of the once-daily dosing interval. Note that improvements in all pulmonary function variables were observed even though all the patients had been receiving stable doses of other ICSs leading up to the time of randomization, when they began using the study drug. Patients treated with mometasone furoate DPI had a much higher probability of continuing in the study without worsening than did those receiving placebo.

Diary data showed low asthma symptom scores at baseline in all the treatment groups, indicating that the participants' asthma had been well controlled with their prestudy ICS medication. These data demonstrated no significant difference between the mometasone furoate DPI treatment groups and indicated superiority over placebo for daytime and nighttime asthma symptoms, PEF, and rescue medication use. In addition, results from the HRQOL assessments demonstrated that the mometasone furoate DPI treatments were superior to placebo. These findings are noteworthy, because few studies have evaluated the effects of ICSs on HRQOL in young children with asthma.

Both mometasone furoate DPI dose regimens were well tolerated, and the incidence, severity, and types of AEs reported in all 3 treatment groups were similar. Most of the AEs were considered by us to be mild to moderate in severity and unrelated to the study drug. The most common treatment-related AEs reported for either treatment group were upper respiratory tract infection (45 patients) and headache (31 patients). Pharyngitis, commonly associated with the use of ICSs, was reported by only 14 individuals (7%) receiving mometasone furoate DPI treatment and 9 (9%) receiving placebo treatment. No patient treated with mometasone furoate DPI reported oral candidiasis, another AE commonly associated with ICS therapy. A review of the 6 serious AEs in this study did not raise any safety concerns, and they were considered unlikely to be related to the study drug. The safety results in the present study are consistent with those observed in previous mometasone furoate DPI studies.[20,21]

A possible limitation in this trial is that there was no evaluation of treatment effects on the hypothalamic-pituitary axis, because evening dosing may have a greater effect than morning dosing on serum and urinary cortisol levels. However, note that in a 1-year safety study[22] of mometasone furoate DPI in children of the same age group as in this study, treatment with mometasone furoate DPI at doses of 100 and 200 μg/d had no significant effects on plasma or urinary cortisol levels.

The mometasone furoate DPI Twisthaler (Asmanex Twisthaler; Schering-Plough, Kenilworth, NJ) delivers uniform doses across a broad range of expected variation in inspiratory flow rates attained by asthmatic patients with different degrees of severity.[23] It also has been shown that children can generate sufficient airflow and maintain correct inhaler technique using the Twisthaler device from one visit to another.[24] Although the success of an ICS treatment regimen depends

primarily on the effectiveness of the medication for asthma control, issues such as ease of inhaler use and the simplicity of the treatment regimen are also important considerations in the selection of ICS therapy, especially for children.[25]

In this study, we demonstrated that mometasone furoate DPI, 100 μg once daily in the evening (delivered as 1 puff), is effective and similar to mometasone furoate DPI, 100 μg twice daily, and that both mometasone furoate DPI dosing regimens were superior to placebo in improving pulmonary function in children with asthma who previously received stable ICS doses. Significant improvements in HRQOL were also observed with both mometasone furoate DPI dosing regimens. These results extend those of a previous pediatric study[18] that found mometasone furoate DPI treatment, 100 μg once daily in the morning, was comparable with 200 μg once daily in the morning. However, there was no twice-daily treatment arm in the previous study. The present study extends the earlier findings by demonstrating that the efficacy of once-daily evening dosing with mometasone furoate DPI is similar to that of twice-daily dosing. In conclusion, mometasone furoate DPI, 100 μg once daily in the evening, is an effective and generally well-tolerated treatment for children with mild-to-moderate persistent asthma.

ACKNOWLEDGMENTS

We thank the study investigators and study coordinators at the investigative sites; Lucy Shneyer, MA, for assistance with statistical analyses; and Ken Kauffman, BSc, and Lisa Ghaly, PharmD, for assistance with manuscript preparation.

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